American Journal of Medical Genetics 83:100–108 (1999)

McCune-Albright Syndrome: Clinical and Molecular Evidence of Mosaicism in an Unusual Giant Patient

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Molecular genetics recently uncovered the mystery of the protean picture of McCune-Albright syndrome by identification of the somatic gain of function mutations in the *GNAS1* gene. Here we present an adult patient with fibrous dysplasia and an endocrinopathy resulting in unusual giant height. The clinical diagnosis in the patient could be confirmed by molecular investigations in tissues involved in the process of fibrous dysplasia. Am. J. Med. Genet. 83:100–108, 1999. © Wiley-Liss, Inc.

KEY WORDS: McCune-Albright syndrome; fibrous dysplasia of bones; gigantism; mosaicism; *GNAS1* gene; visual deterioration; fibrous dysplasia surgery

INTRODUCTION

One and the same disease-causing mutation may result in substantially different clinical pictures. This phenomenon is seen in a growing number of examples [Wolf, 1995, 1997] and raises the problem of what makes a diagnosis: molecular findings or clinical features? The underlying mechanisms are poorly understood with only a few exceptions. Mutations in a G-protein subunit leading to the McCune-Albright syndrome (MAS) are an example in point, and here the mosaicism typically involved offers an explanation of the striking discrepancies between patients.

MAS is caused by activating missense mutations at codon 201 of the *GNAS1* gene encoding the α subunit of the G protein which stimulates the adenylate cyclase ($G_s\alpha$) [Weinstein et al., 1991; Schwindinger et al., 1992; Malchoff et al., 1994; Shenker et al., 1993, 1994; Boston et al., 1994; Dotsch et al., 1996].

Traditionally, MAS is defined clinically by the triad of i) fibrous dysplasia of bone or bones, ii) patchy cutaneous pigmentation, and iii) various hyperfunctional endocrinopathies. Taking into account the existence of incomplete forms, the presence of two signs of the triad are regarded as sufficient for diagnosis [Lee et al., 1986]. On the basis of mutational analyses in a number of patients, however, Shenker et al. [1993] stressed that the consequences of activated Gs, are broader than generally expected and may include further non-endocrine manifestations like hepatobiliary, cardiac, and pancreatic disorders. The typical MAS mutations R201H and R201C, substitutions of histidine or cysteine for Arg^{201}, have also been found in isolated endocrine adenomas [Landis et al., 1989; Lyons et al., 1990] as well as in bone cells from patients with isolated monostotic fibrous dysplasia [Shenker et al., 1995; Alman et al., 1996; Marie et al., 1997].

The diversity of clinical pictures mentioned above is explained by mosaicism; i.e., normal (constitutional) and mutant cells side by side. The phenotype is predicted by the relative number of mutant cells, as well as by the tissues and the body regions involved. The identification of the molecular basis of MAS has elucidated the mystery of its cause, but on the other hand, syndromic boundaries have blurred, and problems in nomenclature and classification are evident.

Anticipating the molecular elucidation of the underlying defect, many years ago Happle [1986] already put forward the concept of a dominant lethal gene defect surviving by mosaicism. The observation that skin pigmentation, the visible consequence of mosaicism, follows the lines of Blaschko was one of his major arguments. The proposed concept was in agreement with the protean variability of clinical manifestations, among them the asymmetric distribution of bone lesions, the variability of endocrine disturbances, the observed incomplete forms, and the sporadic occurrence.

Surprisingly, there are only few clinical reports on patients with MAS in the genetic literature. Here, we present a patient with an incomplete variant of MAS, lacking pigmentation, but with severe bone manifestation of fibrous dysplasia and an unusual giant height. Mutation analysis was performed in different cells from different sites of the body.

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Received 21 September 1998; Accepted 25 November 1998

PATIENT REPORT
Medical History

The male patient is now 40 years old. At age 27 he was referred to the Charité Hospital, Department of Endocrinology, for evaluation of excessive height. At that time polyostotic fibrous dysplasia had been diagnosed radiographically (see below).

According to the patient's report, he always has been the tallest in his age group. His birth length was 61 cm and linear growth continued until age 23. The parents are nonconsanguineous, of average height, and there is no family history of similar bone diseases of any endocrinopathy.

In childhood there was a suspected "osteoma" with surgical intervention of the left maxillary sinus. The patient underwent left femoral stapling at age 12 because of a "cystic lesion." Further medical problems occurred after the age of 26, with progressive hearing loss and progression of bone abnormalities, and at ages 31 and 33 he underwent stapling operations of the left femur again. He had recurrent middle ear inflammations, and sinusites requiring multiple surgeries. Hearing impairment has been treated by a mechanical aid. At age 37 he suffered from a rapid loss of visual acuity in the left eye that occurred in connection with pansinusitis.

Clinical Investigation

On first clinical genetic examination at age 37 acromegalogigantism was obvious. He was 213 cm tall with a disproportionate arm span of 221 cm (Fig. 1). Head circumference measured 64.5 cm and hand length was 25.5 cm. He had an asymmetrical face, coarse facial skin, protuberant supraorbital ridges, hypertelorism, bilateral exophthalmus, and misshapen irregularly spaced teeth (Fig. 2). The thorax was asymmetric, with scoliosis, and the left leg was about 3 cm longer than the right one. There were no hyperpigmented skin areas. Pubic hair was Tanner stage 6.

Endocrine Findings

Hormonal investigations at the time of first admission at age 27 disclosed growth hormone (GH) excess and hyperprolactinemia, with basal serum GH levels ranging from 28 to 50 mIE/liter (normal; <10 mIE/liter), and a serum prolactin (PRL) level increased to 3.344 mIE/liter (normal, <500 mIE/liter). Insulin-like growth factor 1 (IGF-1) was elevated 489 to ng/ml (range, 144–360). Testosterone level was at the lower limit of normal, 9.6 nmol/liter (range, 9–35 nmol/liter). Hypersecretion of GH was not suppressed by oral glucose admission, which, by contrast, paradoxically increased the GH level. Similarly paradoxical increases in GH secretion occurred after thyrotropin releasing hormone (TRH) admission as in luteinizing hormone releasing hormone (LHRH) test. The GH response to insulin was positive. GRF was not elevated. Basal plasma cortisol, luteinizing hormone (LH), follicle stimulating hormone (FSH), parathyroid hormone (PTH), and thyroxin were in the normal range. The patient has been given therapy with Dopaminagonist (Dopergin) since 1986, whereby serum levels of GH, IGF-1, and prolactin were efficiently suppressed.

Radiological Findings

Skull roentgenograms (Fig. 3) show marked sclerotic overgrowth, mottled by small areas of low density, with asymmetrical involvement. The calvarium is markedly thickened especially in the occipital region, and there is a broadened mandible. Except for the sinus frontalis almost all air spaces are not pneumatized. On thorax

Fig. 1. Patient's tall stature.

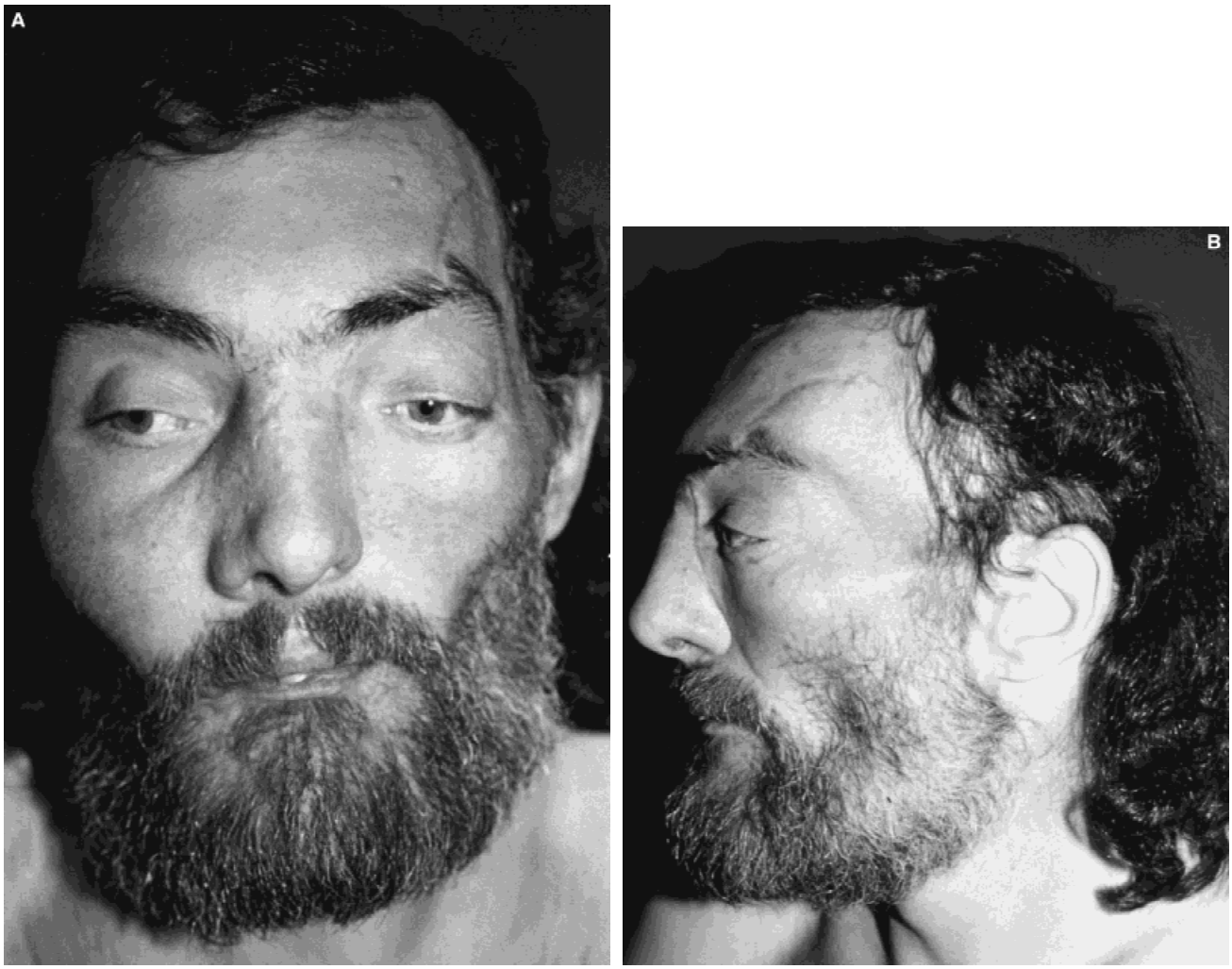

Fig. 2. Frontal **(A)** and left lateral **(B)** facial aspect.

radiograms (Fig. 4) spindle-like enlargements of ribs 6, 10, and 11 on the left side are present. On the long bones the changes are confined to the left side. The left femur (Fig. 5) is misshaped in the regions of his head, neck, and trochanteric region. Here, like in the full upper half of the femur, the spongiosa is mottled by multiple lesions of low density and the corticalis is thinned, whereas in the distal part (Fig. 6) sclerotic changes in the marrow space, such like hyperostosis of the corticalis with expansion to the outer side, are seen. The left tibia (Fig. 7) is irregularly broadened, the marrow space has a ground-glass (smoked) appearance, and circumscribed lytic lesions are seen. The corticalis of the involved long bones is blurred in most parts.

Magnetic Resonance Imaging and Computed Tomography

No adenoma in the pituitary area was disclosed by brain computed tomography (CT) and magnetic resonance imaging (MRI), including MRI with contrast agent enhancement. The pituitary fossa was small and there was now alteration of the gland contour or contrast agent distribution. Asymmetrical involvement of all components of the facial bones was confirmed. The process, more pronounced on the left side, involves the whole skull base with marked hyperostoses of the petrous temporal bones, the upper orbit walls, the clinoides, the clivus, and the sella turcica. Both optic nerves are enclosed by bony masses. The left tympanic cavity is completely shadowed by overgrowthed masses; the right is partially shadowed. CT of the paranasal sinuses disclosed overgrowth masses on the left side occluding the lower nasal meatus, the ethmoid cells, and the sinus maxillaris.

Ophthalmological and Otorhinolaryngological Aspects

Apart from recurrent middle ear inflammations and sinusites, considerable narrowing of the left nasal cavity, existing for many years, did not trouble the patient essentially. Acute visual deterioration, with visual acuity in the left eye being reduced to 0, occurred in October 1995. The massive bone hyperostoses of the base of the skull prevent surgical removal of the bony masses surrounding the nerves. After dexametason therapy vision improved to 0.05. The following data refer to the left eye and left nasal sinuses only. In August 1996 an

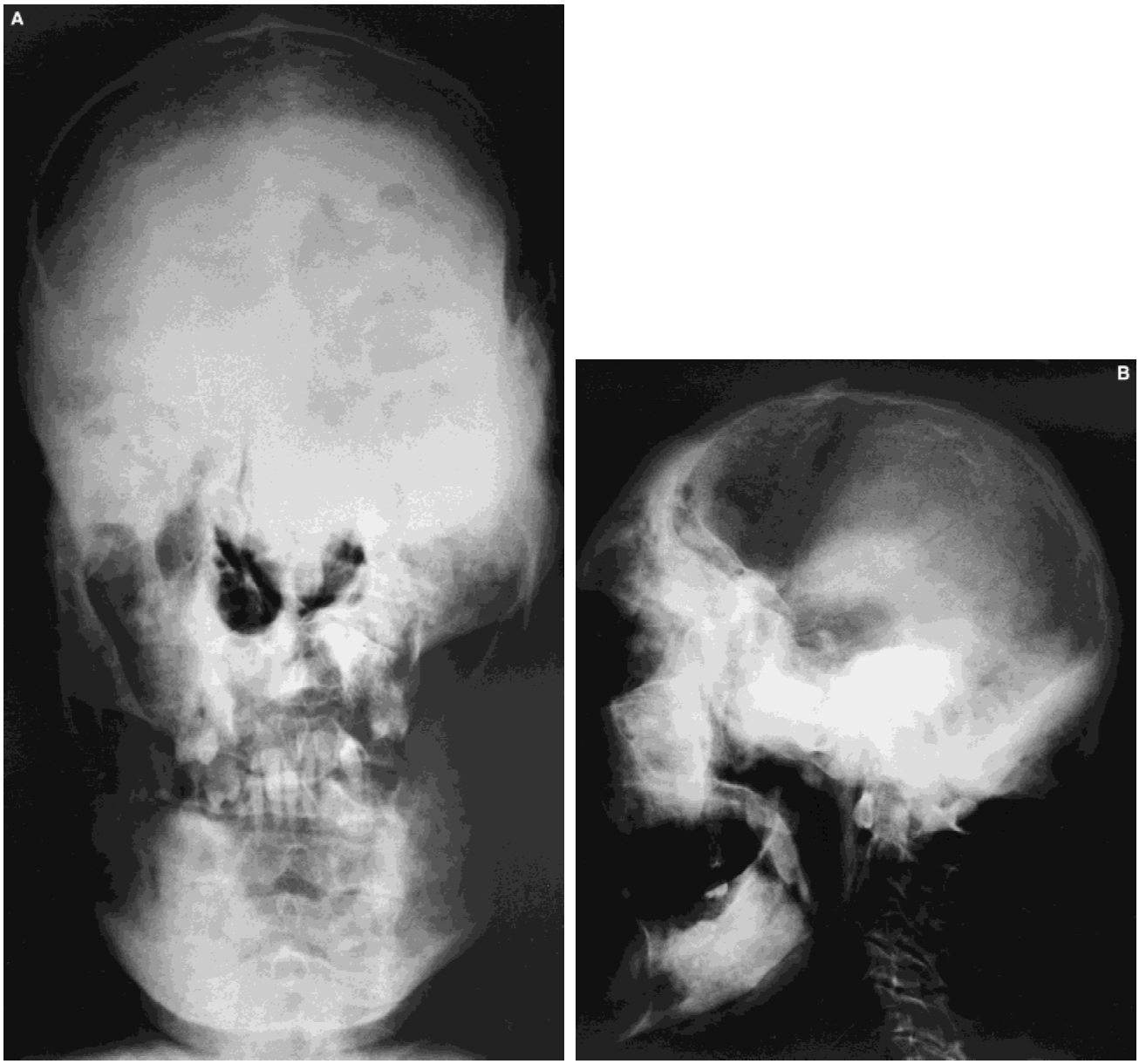

Fig. 3. Anterior-posterior **(A)** and lateral **(B)** radiographs of the skull at age 36.

acute inflammation of frontal and ethmoidal sinuses required emergency operation. After intranasal microscopic and external ethmoidectomy vision improved from 0.05 to 0.6 within three months. In February 1997 visual deterioration reappeared to acuity of 0.04. At this time, because of acute frontal sinusitis and empyema of sphenoidal sinus, open access surgery of frontal, ethmoidal, and sphenoidal sinus was performed. Both, the middle turbinate bone and the lateral wall of the nasal cavity were extremely thickened. Intranasal microscopic surgery of frontal sinus due to acute exacerbation in April 1997 disclosed scar tissue and newly developed fibrous bone barring the connection to the nasal cavity; sphenoidal sinus could not be identified. By intranasal microscopic surgery after CT scan the sphenoidal sinus could be identified and opened. One month later, microscopic surgery of ethnoidal sinus was performed again. At the same time vision returned to normal (1.0) acuity. Two weeks later resection and removal of newly developed fibrous bone at the remains of the middle turbinate bone and nearly complete resection of the anterior wall of the sphenoidal sinus to prevent relapse was performed. In July 1998 intranasal microscopic revision of frontal and ethmoidal sinuses showed completely blocked aperture of the frontal sinus by scar tissue and newly developed fibrous bone. Visual acuity continued to be full (1.0). By current audiometry a slight hearing loss on right and a moderate hearing loss on left, mainly due to conductive failure, was revealed. Histological studies of bone

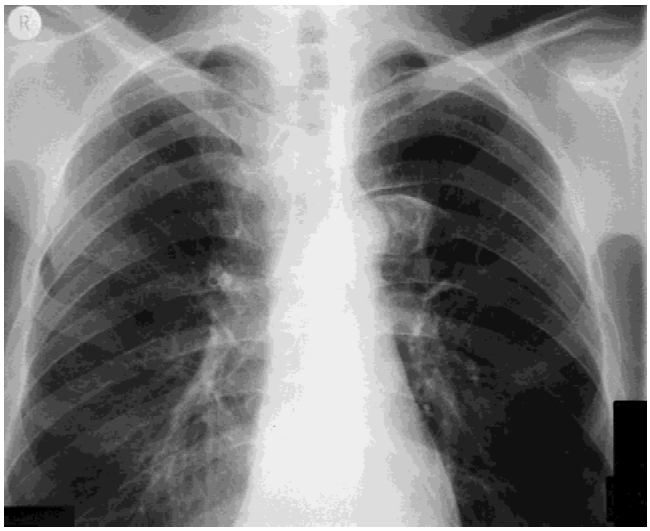

Fig. 4. Thorax radiogram shows involvement of ribs on left side (age 36).

specimens corresponded with the diagnosis of fibrous dysplasia.

MOLECULAR INVESTIGATION

In order to investigate the occurrence of an activating missense mutation in the *GNAS1* gene, and to determine the extent of mosaicism, genomic DNA from a number of specimens from different body parts was analyzed (see Table II). DNA from dysplastic bone specimens obtained in connection with paranasal sinus operations was isolated using the InViSorb™ Forensic Kit (InVi-Tech, Berlin, Germany). DNA from all other tissues and cell cultures was prepared according to standard procedures. Cultures of cells from dysplastic bone specimens were grown in fibroblast standard culturing medium. Skin melanocytes were cultured as described before [Kaufmann et al., 1991].

Polymerase Chain Reaction Amplification

Polymerase chain reaction (PCR) primers were chosen to amplify exons 8 and 9 of GNAS1; for primer sequences see Table I [Williamson, 1995]. About 200 ng of crude DNA were used as template in a total volume of 50 μl of PCR mixture containing dNTPs (200 μM), upstream and downstream primers (500 nM each), 0.1% Triton-X, buffer (10 mM Tris-HCl pH 8.3, 50 mM KCl, 15 mM $MgCl_2$) and 3 U of Taq polymerase (Perkin Elmer Cetus, Weiterstadt, Germany). The following temperature profile was applied for 30 cycles: denaturation at 94°C for 1 min annealing at 58°C for 1 min, elongation at 72°C for 2 min. Thereafter a final extension at 72°C was performed for 5 min. PCR fragments were analyzed by electrophoresis in a 1.2% agarose gel (NEEO Roth, Karlsruhe, Germany) and were visualized with ultraviolet light after ethidium bromide staining. The expected fragment size was 433 bp.

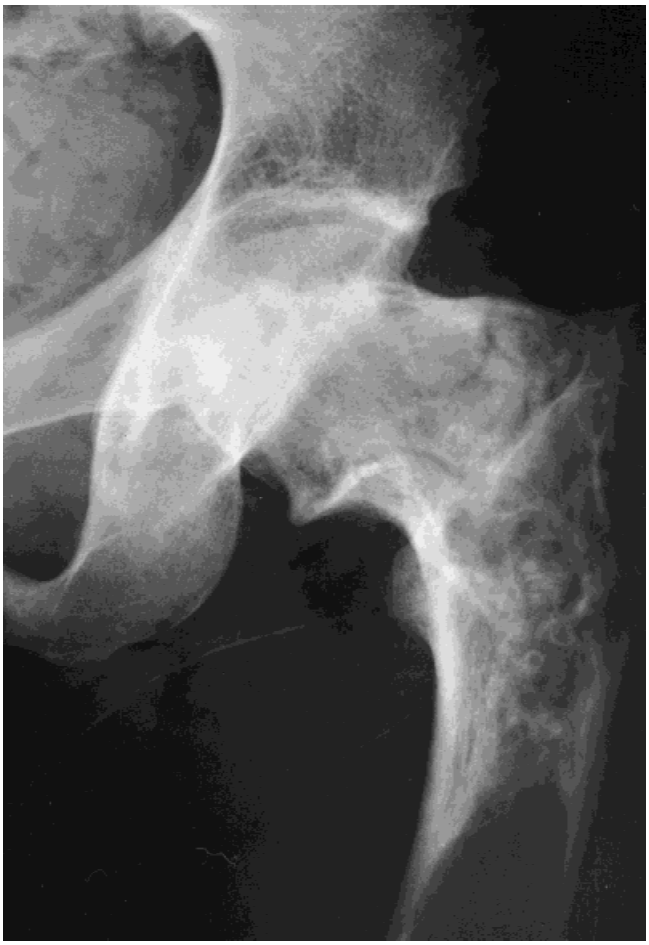

Fig. 5. Radiograph of the left upper femur at age 29 before operation.

DNA Sequencing

Prior to sequencing of the 433-bp PCR product, the corresponding band was isolated from the 1.2% agarose gel (NEEO Roth) and extracted using the QIAquick Gel extraction Kit (Quiagen, Hilden, Germany). The purified PCR fragment was sequenced by the dideoxy chain–termination method (Thermo Sequenase cycle sequencing kit, Amersham, Freiburg, Germany) using sequencing primers labeled with γ-^{33}P-ATP at their 5′ prime end (for sequences and annealing temperatures see Table I).

Slot Blot Oligohybridization

In order to determine the proportion of mutant cells in different tissues, PCR products (see above) were analyzed by allele specific oligohybridization (ASO). Slot blots were hybridized as described by Lyons et al. [1990]. For oligonucleotide sequences see Table I.

The filters were exposed to Biomax MR Scientific Imaging Film (Kodak, Rochester, NY) at −70°C with intensifying screens or were exposed to Fuji Imaging Plate for Bio Imaging Analyzer (BAS III Phospho Imager, Fuji, Düsseldorf, Germany). In the latter case,

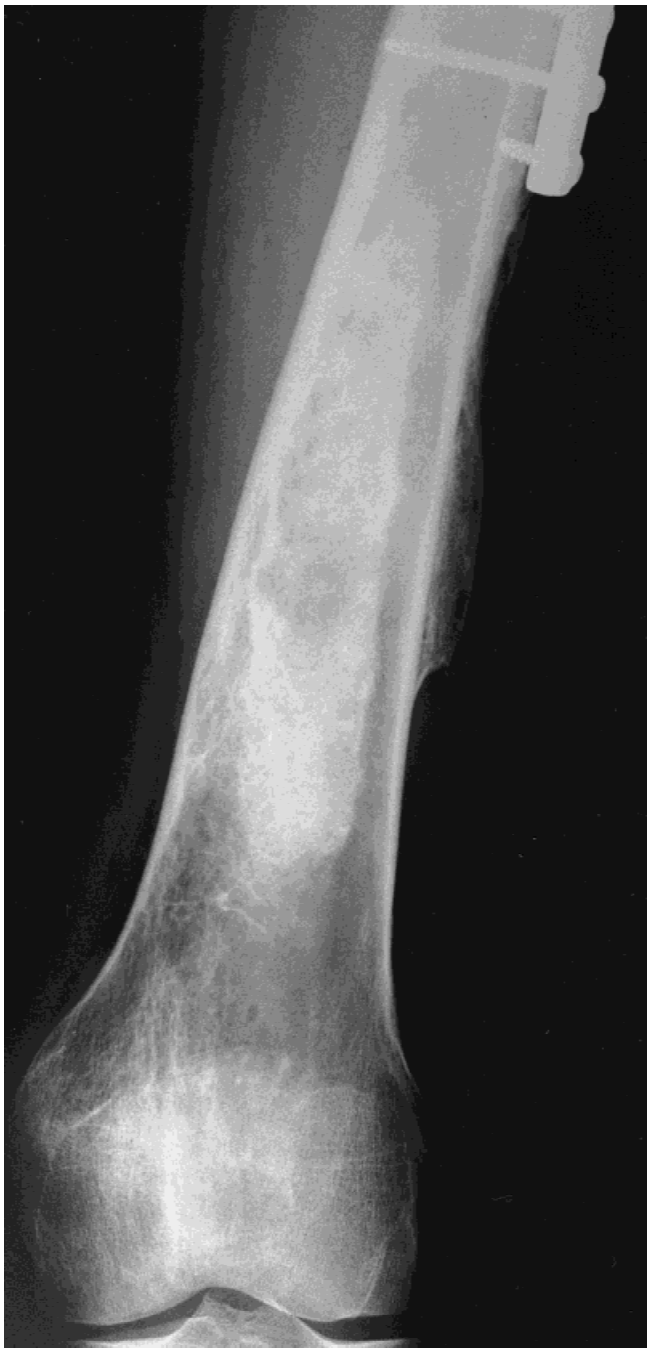

Fig. 6. Radiograph of the lower part of the left femur at age 36.

signals were quantitatively analyzed using the TINA 2.0 software: The signals were integrated and the photo-stimulated luminescence (PSL) determined. The ratio of PSL signals obtained with the mutation representing probe (GSA201His) and the corresponding normal probe (GSA201Arg) was calculated. The ratio value that was obtained with samples of a normal person was considered the reference value and was subtracted from the other values. The fraction of mutant cells in different tissues is shown in Table II.

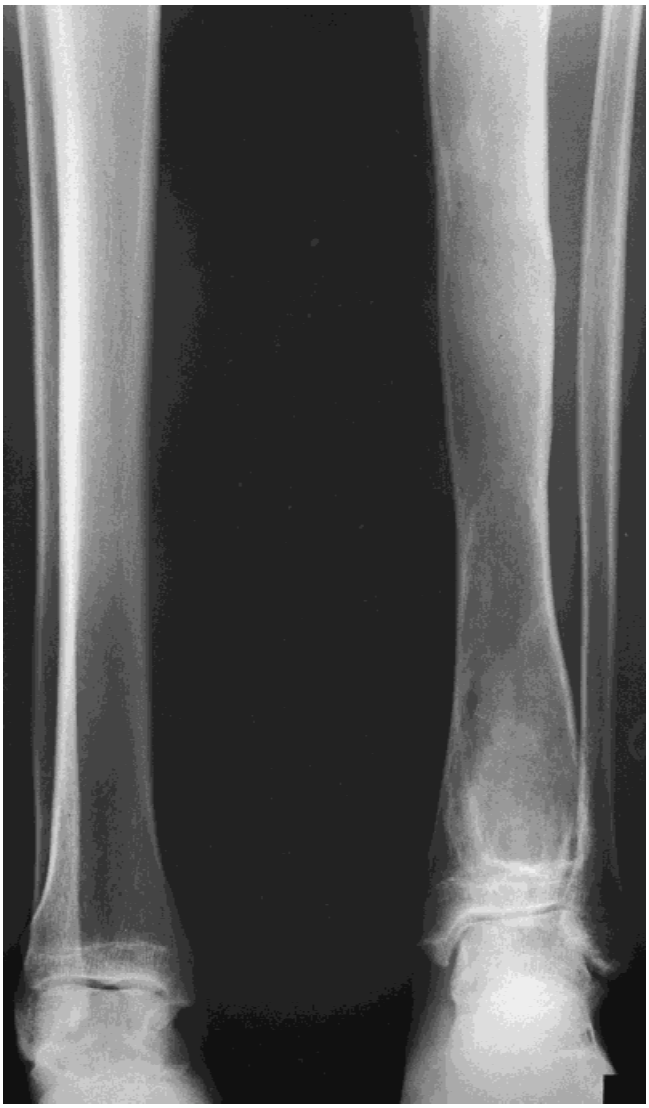

Fig. 7. Radiograph of the lower legs at age 36.

DISCUSSION

Nosological Remarks

The MAS syndrome as a nosological entity was recognized sixty years ago on the basis of the articles of McCune and Bruch [1937] and Albright et al. [1937]. This illustrates a not unusual nosological evolution of a syndrome, initially defined by a few highly specific clinical features.

The original definition of the syndrome, given by Albright et al. [1937] comprised the characteristics "(i) bony lesions which have a marked tendency to be unilateral and which show osteitis fibrosa on histologic examination, (ii) brown nonelevated pigmented areas of the skin which tend to be on the same side as the bone lesions, (iii) an endocrine dysfunction which in females is associated with precocious puberty." The designation "polyostotic fibrous dysplasia" for the bone manifestation was introduced by recognizing the clini-

TABLE I. Primer Sequences

Primer name	Sequence	Annealing temperature	Purpose
GNAS1F	CCCCTCCCCACCAGAGGACTCTGA	58°C	PCR primers
GNAS1R	AGAGCGTGAGCAGCGACCCTGATC	58°C	
GS8F	TAGATTGGCAATTATTACTG	44°C	Sequencing primer
GS9F	TTTCTTGACATTCACCCCAG	54°C	Sequencing primer
GSA201Arg	TTCGCTGCCGTGTCCTGACT		Oligohybridization
GSA201His	TTCGCTGCCATGTCCTGACT		

cal and histological identity with the bone disorder delineated by Hunter and Turnbull [1931], Jaffé [1933], and Lichtenstein [1938] which may occur as an isolated condition [Falconer et al., 1942]. In their review of fibrous dysplasia, Lichtenstein and Jaffé [1942] concluded on the basis of microscopic examinations that fibrous dysplasia of only one bone, often termed as "localized osteitis fibrosa," represents a mild (i.e., monostotic) form of the same skeletal lesion as seen in polyostotic fibrous dysplasia. They postulated that the same basic defect may result in a variable expression of fibrous bone lesions, and may lead additionally to nonskeletal manifestations. The latter includes most common skin pigmentations, and (in females) premature sexual maturation as described by Albright and colleagues, but also hyperthyroidism present in McCune's original patient [1937]. With reference to associated (cardiovascular and renal) anomalies, Lichtenstein and Jaffé [1942] pointed out that the syndrome probably represents a "museum of developmental abnormalities." The variable involvement of endocrine tissues has been a source of considerable debate and confusion. It became known that precocious puberty is common but not always present in girls and it may be seen also in boys [Falconer et al., 1942]. Subsequently, further endocrinopathies were described in connection with MAS. With falling frequencies elevated sex hormones, hyperthyroidism, extensive secretions of growth hormone, prolactin, and cortisol have been associated [for review, see Ringel et al., 1996]. Hyperparathyroidism is not associated except in a few convincing instances [Benedict, 1962; Caudill, et al., 1977; Cavanah and Dons, 1993]. However, the bone lesions are reminiscent of the "brown tumors" seen in the generalized osteitis fibrosa (von Recklinghausen's form) which occur in primary hyperparathyroidism. The endocrinopathies in MAS are characterized by autonomous excessive hyperfunction of hormonally responsive cells [DiGeorge, 1975; Foster, 1993] and share the involvement of cells which respond to signals through activation of the adenylate cyclase system, the enzyme system that catalyzes cyclic adenosine monophosphate (cAMP) formation [Mauras and Blizzard, 1986, Lee et al., 1986]. It was shown that fibrous dysplasia in MAS reflects cAMP-induced changes in osteoblastic cells which are the result of a *GNAS1* mutation in cells of the osteogenic lineage [Riminucci et al., 1997]. In primary hyperparathyroidism, the same pathway for development of fibrous dysplasia may be explained by hormonal-dependent cAMP excess. Further signal transductions than via cAMP are postulated to explain hepatobiliary disease, cardiac disease, and other nonendocrine abnormalities like thymid hyperplasia, gastrointestinal polyps, and neurodevelopmental disorder in a severe form of MAS [Shenker et al., 1993].

Moreover, heterogeneity of MAS syndrome has been proposed recently based on the finding of functionally normal $G_s\alpha$ protein in a patient with pituitary macroadenoma and polyostotic fibrous dysplasia [Gessl et al., 1994]. Furthermore, absence of a *GNAS1* mutation has been persuasively documented in a patient with primary hyperparathyroidism and polyostotic fibrous dysplasia [Hammami et al., 1997]. Last but not least, familial hyperparathyroidism with fibro-osseous tumors restricted to the jaw (OMIM *145001) has been mapped to the long arm of chromosome 1 [Szabo et al., 1995].

TABLE II. Results of Mutation Analysis by Allele Specific Oligohybridization

Tissue specimens	Proportion of mutant cells (%)
Buccal smear	0
Blood	0
Skin melanocytes, left body side	0
Skin melanocytes, right body side	0
Middle nasal concha (frozen)	45
Frontal sinus, anterior wall (frozen)	12
Frontal sinus, anterior wall (cell culture)	2
Frontal sinus, posterior wall (frozen)	10
Frontal sinus, posterior wall (cell culture 1)	0
Frontal sinus, posterior wall (cell culture 2)	84
Frontal sinus, roof (frozen)	6
Middle nasal concha, formalin fixed	39
Negative control	0

Patient

The clinical diagnosis of MAS in this patient is based on the polyostotic fibrous dysplasia and the endocrinopathy, characterized by autonomous behavior. In addition, there was positive molecular evidence by demonstration of the characteristic mutation $Arg^{201} \rightarrow His$ in exon 8 in one allele of the *GNAS1* gene.

The hormonal characteristics in this patient are similar to those of other acromegalic patients with MAS described previously. These are indistinguishable from those of patients with isolated pituitary tumors. Hypersecretion of growth hormone and prolactin were marked and there was no decrease of the GH level by oral glucose tolerance test (OGTT), which caused paradoxical increase, as did TRH. Hyperprolactinemia occurs in over 50% of MAS patients with elevated GH and is more frequent than in patients with isolated growth

TABLE III. Patients With Body Height Over Percentile 97 Reported in the Literature

Sex	Age (years)	Body height (cm)	Prolactin (ng/ml) (normal <200 ng/ml)	Reference
M	42	200	Not mentioned	Powell, 1976
F	14 9/12	183	2,000	Cuttler et al., 1989
M	38	203	234	Pacini et al., 1987
M	42	203	6,700	Chanson et al., 1994
M	18	198	430–480	Chanson et al., 1994
F	17	182	500–560	Chung et al., 1983
F	35	180	2,700–3,200	Cremonini et al., 1992
M	21	202	Not mentioned	Firat and Stutzman, 1968

hormone producing pituitary tumors [Ringel et al., 1996].

In this patient a pituitary tumor could not be detected by repeated CT and MRI scans. This is not unexpected, as evidence of a pituitary adenoma was found only in 64% of MAS patients with GH excess by Chanson and colleagues [1994]. They pointed out that skull thickening (in our patient the sella turcica was narrowed by bony overgrowth) compromise the interpretation of CT scans, but MRI is sufficient to distinguish clearly adenomatous pituitary and fibrous bone tissue. Pituitary morphology in patients with MAS showed either a normal pituitary or an adenoma, nodular hyperplasia, or mammosomatotropic hyperplasia [Chanson et al., 1994, Ringel et al., 1996]. It is unknown whether the autonomous tumors in MAS result from the proliferation-inducing effect of the GNAS1 mutation alone or if a secondary oncogenic event is needed [Burton et al., 1991].

The patient's tall stature is of special interest. Accelerated linear growth is frequent in childhood in patients with MAS. Most patients, however, achieve normal or somewhat decreased adult height [Lee et al., 1986; Cavanah and Dons, 1993]. Very short adult height occurring in some patients is a well-known feature since Albright's classical report and was associated with puberty at an extremely young age. Adult gigantism seems to be an unusual manifestation in MAS, although GH excess is a frequently associated endocrinopathy occurring in nearly 25% [Ringel et al., 1996] of patients.

Nerlich and his colleagues [1991] reported polyostotic fibrous dysplasia in the skeleton of the 2.35-m tall "Tegernsee giant" who died 1876 at age 25. The authors discussed the diagnosis of MAS but called it in question because of the tall stature. As pointed out in a reply by Schwindinger and colleagues [1991], the association of polyostotic fibrous dysplasia and gigantism is not unexpected on the basis of molecular findings in MAS. In the same article, however, they mentioned an adult patient, reported on later [Schwindinger et al., 1992], who was only 122 cm tall.

Depending on the random affected endocrine tissues a polymorphic picture of endocrinopathies can result [Cavanah and Dons, 1993]. The endocrinopathies are very different in respect to their influence on growth velocity. GH and PRL excesses both show growth-promoting effects, the former directly and the latter by enabling a longer growth period through pubertal delay. Other endocrinopathies like sexual precocity, hyperthyroidism, and Cushing syndrome are associated with advanced skeletal maturation and premature epiphyseal closure. So, naturally, this means that without therapeutic interventions possible today, the adult height in patients with MAS may include all variations of a great spectrum, with dwarfism and gigantism at the extreme points.

The possible overlap of different endocrinopathies is obvious when the frequencies of occurrence in patients with MAS are taken into account: precocity 66%, hyperthyroidism 33%, GH excess 25%, and Cushing syndrome 9% [for frequencies, see Ringel et al., 1996]. Therefore, coexisting endocrinopathies may result in normal adult height.

Reviewing the literature, we found some more reports on patients with MAS and a giant (over percentile 97) adult body height (Table III). In nearly all patients of tall stature, GH excess was associated with hyperprolactinemia. This is the case in our patient too.

By examination of DNA samples from different tissues we found marked differences in the proportion of the Arg^{201} mutation compared with the wildtype allele. The mutation was detected in dysplastic bone only, but not in patient's peripheral blood leukocytes or in different (but not hyperpigmented) skin biopsies, including one from the affected body side. The percentage of the mutant allele in the uncultured dysplastic bone specimens ranged from 2 to 45%. After cell culturing, however, the mutant allele level showed an even larger difference (0–84%) in the same starting material. This may be due to accidental selection of both cells bearing the mutation or normal cells. All together our data support an underlying genomic mosaic and indicate that mutation analysis can fail, if the "wrong cells" are investigated.

ACKNOWLEDGMENTS

The authors thank the patient for his cooperation. Thanks are also due to Ingrid Beilfuß and Ingrid Barth for technical assistance, and Thomas Wienker for helpful discussion.

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